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'Hypertension' and 'microalbuminuria': The bell tolls for thee

JP Forman[1,2] and BM Brenner[1,2]

[1]Harvard Medical School, Boston, Massachusetts, USA and [2]Renal Division, Brigham and Women's Hospital, Boston, Massachusetts, USA

Since the terms 'hypertension' and 'microalbuminuria' were first defined, data from numerous studies have documented the continuous, rather than dichotomous, relation between blood pressure, albumin excretion, and cardiovascular disease. Lower blood pressures, down to at least 115/75 mmHg, and lower albumin excretions, below an estimated 2 mg/day, are associated with less cardiovascular risk. We hypothesize that the abundances of modern civilization superimposed on the Paleolithic genotype of humans, which has not substantially changed in the last 10 000 years, have considerably shifted the 'normal' values for blood pressure and various biochemical indices such as albuminuria still found in today's stone-aged cultures to the 'neo-normal' values observed today in the rest of the modern world. Defining a large portion of the population as 'normal' based upon these dichotomous 'neo-normal' standards is not supported by the data, and therefore seems unjustifiable. We propose that the medical community consider abandoning the terms 'hypertension' and 'microalbuminuria' in favor of 'blood pressure-associated' and 'albuminuria-associated' disease.

Kidney International (2006) **69,** 22–28. doi:10.1038/sj.ki.5000056

KEYWORDS: hypertension; microalbminuria; cardiovascular; blood pressure; albuminuria; origins of disease

Correspondence: *JP Forman, Channing Laboratory, 3rd floor; 181 Longwood Avenue, Boston, MA 02115, USA. E-mail: jforman@partners.org*

Sources of support for this manuscript: none.

Received 28 September 2005; accepted 3 October 2005

WHAT IS NORMAL?

The terms 'hypertension' and 'microalbuminuria' imply a threshold level for blood pressure and albuminuria below which disease risk is not seen. This terminology defines a large group of people as normal, and ignores the impact that even minor variations of blood pressure and albumin excretion may have on disease within the so-called normal range. In this article, we propose that the medical community consider abandoning these terms, discuss blood pressure- and albuminuria-related disease risk, and review treatment targets for associated cardiovascular and renal protection.

HISTORY

History of hypertension and the joint national committee

Following the first measurement of blood pressure in the femoral artery of a horse by Hales in 1733, and the recognition by Bright in 1827 that arteriosclerosis, shrunken and fibrotic kidneys, and cardiac hypertrophy were clinically linked, elevated blood pressure as a distinct entity was initially championed by T Clifford Allbutt in 1893, who was also the first to use the word 'hyperpiesia', or hypertension. Early pharmaceuticals were first used to treat malignant hypertension in the 1940s and 1950s, with significant improvements in outcomes. However, whether 'essential' hypertension (a term coined by Janeway in 1904) was a benign condition or one that would benefit from treatment was not answered until the VA Cooperative Studies published in 1967 and 1970.

Subsequently, the National High Blood Pressure Education Program, developed in 1972 by the National Heart, Lung, and Blood Institute, published the very first report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC 1) in 1977.[1] This report, whose bibliography included solely the VA study published seven years earlier, recommended intervention in patients with diastolic blood pressures (DBPs) greater than or equal to 90 mmHg; DBP $>$ 104 mmHg warranted drug therapy, whereas DBP 90–104 mmHg could initially be approached with risk factor reduction. Although the 1980 guidelines (JNC 2) defined mild, moderate, and severe hypertension along the same cutoffs of DBP, JNC 3 in 1984 included systolic blood pressure (SBP) ('normal' SBP being $<$140 mmHg) in the definition.[2,3] Subsequent JNC guidelines in 1988, 1993, and 1997 adhered to the same definition of 'normal' blood pressure, with the recognition by JNC 5 of

a 'high normal' category, and by JNC 6 of an 'optimal' category within the normal range.[4–6]

The seventh report of the JNC recognized the associations between even small increments above 115/75 mmHg with cardiovascular outcomes, retreating somewhat from older definitions by reclassifying the 'high normal' group as 'prehypertension' instead.[7] Based upon the fourth National Health and Nutrition Examination Survey (1999–2000 NHANES), an estimated 58% – the majority of all adults in the United States – have abnormal blood pressure as defined by JNC 7 categories of prehypertension or hypertension.[8] Given the continuous association between blood pressure and risk as well as the absence of the J-curve, future progressive redefining of normality is all but assured, thus making the term 'hypertension' – a term which implies dichotomy – seem unjustifiable.

History of microalbuminuria

The term 'microalbuminuria' first appeared in the medical literature in 1981, used by Viberti and colleagues and Svendsen and colleagues to describe the presence of albuminuria below the detection limit of a standard dipstick, but at a level that was highly predictive of future overt proteinuria in diabetic patients.[9–11] Microalbuminuria became an official part of the medical lexicon in 1985, defined as an albumin excretion rate between 20 and 200 μg/min. Although the lower bound was chosen because 95% of 'normal' individuals had excretion rates below that limit, it was recognized that risk of progression to nephropathy was elevated among diabetics in the 'high normal' range.[12] Similar to the relationship between blood pressure and risk of cardiovascular events, mounting evidence indicates a continuous relationship between albumin excretion and risk. And like blood pressure, the concept of a threshold level to define normality is inconsistent with epidemiological data.

HYPOTHESIS

'Normal' from the vantage point of primitive vs modern anthropomorphism

The anthropologic record indicates that before the last 5000 to 10 000 years, *Homo sapiens* was considerably smaller in stature and body weight,[13] and presumably characterized by lower blood pressure, glomerular filtration rate, and cholesterol than are commonplace today. Stone-age tribes studied today confirm the anthropomorphic and biochemical patterns predicted for earlier humans.[14–24] At the start of the Holocene 10 000 years ago, the earth's climate warmed, allowing people to establish villages and invent the basic tools of agriculture, herding, and metallurgy. Humans began to grow considerably in stature and body mass, and our 'paleo-normal' physiologic values, perhaps lower than 90 mmHg for SBP, 100 mg/dl for total serum cholesterol, increased substantially to our current 'neo-normal' base of reference.[14,16,18,20–23] Neo-normal values can then be regarded as excessive to our paleophysiological and genetic heritage; hence, the benefit in risk reduction seen with therapies that return values closer to our original set points.

The general concept that our genetic heritage has been greatly outpaced by our modern environment, thus leading to increased weight, blood pressure, insulin resistance, and other medical problems, is forwarded by the 'thrifty-genotype' hypothesis.[25] 'Thrifty' genes, which predispose us to low metabolic rates and salt conservation, evolved to preserve energy and blood pressure in Paleolithic humans faced with shortages in energy, salt, and with high physical demands.[26] Now faced with an abundance of food and sedentary lifestyles in modern humans, these thrifty genes have become associated with disease.

Isolated or 'primitive' cultures may arguably be the nearest representation of 'normal' human reference populations with respect to our genetic heritage. Many such populations have been identified, whose average blood pressures and cholesterol levels are very low, accompanied by low rates of cardiovascular disease.[27] Furthermore, blood pressure and serum cholesterol values do not increase with age as is commonly observed outside these isolated cultures. Regardless of the explanation for such phenomena, whether it be low salt consumption[28] or high intake of cocoa,[29] free-living people with average lifetime blood pressures of 90/60 mmHg are not hypotensive, but rather healthy and free from the cardiovascular morbidity and mortality so prevalent elsewhere. Thus, from the vantage point of primitive anthropomorphism, almost every adult in the United States and indeed most of the world has abnormally high blood pressure.

MISCONCEPTIONS

The cholesterol example

The National Cholesterol Education Program does not define a cutoff value for 'hypercholesterolemia'.[30] Rather, the evidence-based guidelines for the prevention of cholesterol-associated disease include individualized treatment goals. For example, the treatment goal for a diabetic is different than the goal serum cholesterol level for someone with no cardiovascular risk factors. Furthermore, results from current and future trials will likely lead to adjusted guidelines and lower targets.

Epidemiologic evidence supports a continuous log-linear relationship between total serum cholesterol, low-density lipoprotein (LDL) cholesterol, and the risk of coronary heart disease in the general population.[31,32] The continuous relationship persists down to an LDL as low as 40 mg/dl, with every 30 mg/dl higher LDL associated with a 30% increase in the relative risk of coronary heart disease.[31] Newer randomized trials similarly support the notion that lower is better. Data from the Heart Protection Study showed that all subgroups of high-risk individuals, including those whose starting pretrial LDL was <100 mg/dl, benefited from LDL-lowering therapy.[33] These results were echoed by the PROVE IT study (Pravastatin or Atorvastatin Evaluation and Infection – Thrombolysis in Myocardial Infarction 22) in which a significantly lower risk of death or cardiovascular morbidity was obtained in high-risk patients with an achieved LDL of 62 mg/dl compared to 95 mg/dl.[34]

Strikingly similar scenarios exist for blood pressure and albuminuria, as will be discussed. Taking a page from the

cholesterol playbook, the appropriate approach to blood pressure and urinary albumin excretion would be abandonment of 'hypertension' and 'microalbuminuria', and adoption of evidence-based treatment goals.

Blood pressure-associated disease

Blood pressure and blood pressure-associated disease should replace 'hypertension' in our lexicon. As pointed out by Rose,[35] and subsequently quoted by MacMahon *et al.*,[36] high blood pressure can be operationally defined as the level at which further reductions do not lead to additional benefits. Treatment targets thus may differ among different comorbid groups, and targets are likely to change with future randomized trials of more intensive blood pressure lowering.

The misconception of the J-curve

In 1978, Anderson reported that re-examination of the Framingham Cohort unsmoothed blood pressure data revealed no additional benefits to DBP < 90 mmHg *vis-a-vis* cardiovascular disease.[37] A year later, Stewart[38] proposed the concept of the J-curve, and this was followed by confirmation of the J-curve for DBP in participants of several blood pressure-lowering trials.[39–42] Arguments against the J-curve hold that the increase in events at the lower end of the spectrum are, in fact, a result of reverse causality, in that coexistent comorbid disease such as congestive heart failure or vascular disease is responsible for both the higher risk of events and lower SBP or DBP.

Indeed, a 2004 examination of Framingham data implicates pre-existing cardiovascular disease as an explanation of higher risk at lower DBPs. The authors reported that the risk of cardiovascular events at DBP < 90 mmHg was higher only among those with SBP > 140 mmHg, suggesting that the J-curve for DBP may be explained by a widened pulse pressure and high SBP; when SBP was < 140 mmHg, lower DBP decreased the risk of cardiovascular disease.[43] Moreover, many other trials have failed to show a J-curve,[44–46] whereas others demonstrating a J-curve could not fully account for baseline comorbidity such as the severity of pre-existing heart failure and vascular disease.[41,42] Finally, in an analysis that combined individual data from almost one million participants with no baseline cardiovascular disease from 61 prospective studies, there was a linear association between both SBP and DBP and risk of cardiovascular mortality down to 115 mmHg SBP and 75 mmHg DBP. At blood pressures below these values, the risk of cardiovascular mortality was even lower.[47]

The misconception of 'normotension'

The linear relationship between blood pressure and cardiovascular death just mentioned is reminiscent of the association between cholesterol and risk of coronary heart disease. Down to a blood pressure of 115/75 mmHg, every 10 mmHg lower usual systolic or 5 mmHg lower usual diastolic pressure is associated during long-term follow-up with a 40% reduction in risk of death from stroke and a 30% reduction in risk of death from ischemic heart disease.[47] These findings are consistent with other observational studies,[48] and once again argues that our current definition of normal be re-evaluated.

Results from randomized controlled trials have confirmed that a further reduction in blood pressure among 'normotensive' individuals indeed lowers the risk of cardiovascular events (Table 1). These studies include populations where the

Table 1 | Randomized trials of blood pressure reduction involving high-risk 'normotensive' individuals

Study	Population (normotensive subset)	Entry BP (mmHg) (normotensive subset)	Intervention	BP reduction (mm/Hg)	Outcome	Risk reduction (normotensive subset) (%)
HOPE	Known vascular disease or diabetes plus one other CV risk factor *n*=4942	Not given (presumed <140/90)	Ramipril	3/2 (study visits) 10/4 (24 ABPM)	Composite of CV death, nonfatal stroke, nonfatal MI	20
PROGRESS[a]	Prior stroke or TIA *n*=3189	136/79	Perindopril or Perindopril plus indapamide	5/3 (single drug) 12/5 (combination)	Recurrent stroke Composite of CV death, nonfatal stroke, nonfatal MI	27 24
EUROPA[a]	Known CAD *n*=8906	Not given (mean for entire cohort 137/82)	Perindopril	5/2	Composite of CV death, nonfatal MI, cardiac arrest	20
CAMELOT[a]	Angiographically confirmed CAD *n*=1991	129/78	Amlodipine or Enalapril	5/2.5	Composite of CV death, MI, stroke, TIA, PVD, CHF, ACS, cardiac arrest	31 (amlodipine) 19 (enalapril, NS)
ABCD	Type II DM *n*=480	136/84	Nisoldipine or Enalapril	9/6	Stroke	70

ABCD=Appropriate Blood pressure Control in Diabetes; ABPM=24 h ambulatory blood pressure monitoring; ACS=acute coronary syndrome; CAD=coronary artery disease; CAMELOT=Comparison of Amlodipine; CHF=congestive heart failure; CV=cardiovascular; DM=diabetes; EUROPA=EURopean trial On reduction of cardiac events with Perindopril with stable coronary Artery disease; HOPE=Heart Outcomes Prevention Evaluation; MI=myocardial infarction; NS=nonsignificant; PVD=peripheral vascular disease; PROGRESS=Perindopril pROtection aGainst REcurrent Stroke Study; TIA=transient ischemic attack.

[a]The PROGRESS and EUROPA trials defined hypertension as BP ⩾ 160/90 mmHg; the CAMELOT defined hypertension as DBP ⩾ 100 mmHg. However, mean BP in PROGRESS and CAMELOT were 136/79 mmHg and 129/78 mmHg, respectively. In EUROPA, the BP for the entire cohort (both hypertensive and normotensive) was 137/82 mmHg – presumably the normotensive group had a lower mean entry BP.

absolute risk of cardiovascular outcomes is high, such as diabetes,[45,49,50] coronary artery disease,[46,49,51] and cerebrovascular disease,[52] a requirement necessary to achieve adequate statistical power during the relatively short duration of a randomized trial.

Type II diabetics with baseline blood pressures <140/80 mmHg were randomized in the normotensive ABCD (Appropriate Blood pressure Control in Diabetes) trial to placebo or active treatment with either enalapril or nisoldipine.[45] During five years of follow-up, the incidence of strokes was 70% lower in the active treatment group ($P = 0.03$) compared to the placebo group (mean BP 137/81 mmHg compared to 128/75 mmHg in the active treatment group).[45] Among a subset of these patients with peripheral vascular disease in addition to diabetes, the aggressive blood pressure treatment also reduced the risk of a combined cardiovascular end point of CV death, nonfatal stroke, and nonfatal myocardial infarction by approximately two-thirds.[50] Treatment of 'normotensive' diabetics with ramipril in the HOPE (Heart Outcomes Prevention Evaluation) study also resulted in a reduction of cardiovascular events.[49]

The CAMELOT (Comparison of AMlodipine vs. Enalapril to Limit Outcomes of Thrombosis) study randomized 1991 individuals with angiographically confirmed coronary artery CAMELOT vs. Endapril to Limit Outcomes of Thrombosi (disease and a mean baseline blood pressure of 129/78 mmHg to either placebo or active treatment (10 mg of amlodipine or 20 mg of enalapril).[46] Active treatment resulted in a blood pressure separation from placebo of about 5/2.5 mmHg. During 2 years of follow-up, the occurrence of the cardiovascular end point was reduced by 30% with amlodipine therapy. Enalapril therapy lowered the risk by 20%, but this was not statistically significant. Among participants with known coronary artery disease in the EUROPA (EURopean trial On reduction of cardiac events with Perindopril with stable coronary Artery disease) study, active treatment led to a 20% lower cardiovascular event rate, along with an average 5/2 mmHg reduction in blood pressure compared to placebo; the results were consistent whether participants were 'hypertensive' or 'normotensive' at baseline.[51]

The PROGRESS (Perindopril pROtection aGainst REcurrent Stroke) Study included 3189 'normotensive' participants with a prior stroke history and mean entry blood pressure at baseline of 136/79 mmHg.[52] They were randomized to either perindopril (resulting in a 5/3 mmHg fall in blood pressure), a combination of perindopril and indapamide (resulting in a 12/5 mmHg fall in blood pressure), or placebo. All vascular events were reduced by 24% with active therapy in this 'normotensive' group. However, combination therapy, concomitant with its greater effect on blood pressure, appeared more effective: combination therapy reduced the risk of recurrent stroke by 42% in these individuals.

Participants of the HOPE study had known cardiovascular disease or diabetes at baseline, and 53% had blood pressures <140/90 mmHg at entry.[49] Blood pressure separation with ramipril compared to placebo was 3/2 mmHg at the four study visits, but in fact may have been more substantial given the results of a substudy that measured ambulatory blood pressure.[53] Among the 'normotensive' group, the combined cardiovascular end point was reduced by 20% with active treatment.

Whether targeting a lower blood pressure goal of <130/80 mmHg compared to <140/90 mmHg reduces the risk of cardiovascular outcomes in another high-risk population, namely those with nondiabetic chronic kidney disease, remains undetermined. So far, three randomized trials have examined this question.[54–56] Although two did not show a significant benefit to lower targets within the normal range, the study with the longest follow-up and highest degree of statistical power demonstrated a significant reduction in both end-stage renal disease and all-cause mortality.[56] The MDRD (Modification of Diet in Renal Disease) Study achieved a blood pressure separation of approximately 8/3 mmHg (126/77 vs 134/80 mmHg) over 2 years; during an average of 6 years of follow-up, end-stage renal disease and all-cause death was reduced by 23% in the group with lower blood pressure.[56]

Thus, the current evidence provides us with both the *observation* that the risk of cardiovascular events follows a linear relationship with blood pressure and with the clinical trial *experimentation* that achieving further blood pressures reductions within the so-called 'normal' range indeed reduces the risk of cardiovascular events.

Albuminuria-associated disease

'Microalbuminuria' is another term that should now be eliminated from our lexicon, as there are ample data to suggest that albuminuria in the 'normal' range carries significant risk of vascular events.

The misconception of normoalbuminuria

Any degree of non-negligible albuminuria bears a significant risk for cardiovascular events. *Post hoc* analyses of randomized trials in high-risk individuals as well as community-based cohort studies all indicate that incremental increases in albuminuria within the 'normal' range carry higher risks of cardiovascular morbidity and mortality, elevations in blood pressure, and even noncardiovascular death (Table 2).[57–65] Moreover, data from the Steno Diabetes Center in type I diabetics, as well as *post hoc* analyses of RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) data in patients with type II diabetes, LIFE (Losartan Intervention For Endpoint) reduction in hypertension data in patients with 'hypertension', and African American Study of Kidney Disease and Hypertension data in African Americans with nondiabetic chronic kidney disease all suggest that the degree of albuminuria reduction in response to treatment is a primary determinant of both renal and cardiovascular outcomes.[66–70]

Table 2 | Risk of cardiovascular events associated with albuminuria within the 'normal' range

Study	Population	Outcome	Risk assessment
Post hoc analyses of randomized trials in high-risk individuals			
HOPE	Known vascular disease or diabetes plus one other CV risk factor *n*=9043	Composite of CV death, nonfatal stroke, nonfatal MI	Risk began to increase with excretion rates above an albumin/creatinine ratio as low as 1.9 mg/g Risk increased 6% for every 4 mg/g increment
LIFE	Hypertension and LVH *n*=8206	Composite of CV death, nonfatal stroke, nonfatal MI	Risk began to increase with excretion rates above an albumin/creatinine ratio as low as 2.2 mg/g (for e.g., 60% increased risk associated with 14–22 mg/g compared to <2.2 mg/g Risk increased 55% for every 10-fold increment
Community-based cohort studies			
PREVEND[a]	Community residing adults in Groningen, The Netherlands *n*=40 548	CV death Non-CV death	Risk of CV death increased 29% for every twofold increase in urine albumin concentration (on early morning sample) Risk of non-CV death increased 12% for every twofold increase in urine albumin concentration
Copenhagen Community Cohort	Community residing older adults (aged 50–89 yr) without prevalent heart or renal failure *n*=626	Composite of CV death, MI, stroke, TIA, unstable angina, CHF	Risk was 2.3-fold higher among those with albumin/creatinine ratio >18.4 mg/g compared to those $\leqslant 18.4$ mg/g
Copenhagen City Heart Study	Individuals without prior CHD drawn from community residing adults in Copenhagen *n*=2762	CHD and death	Compared to $\leqslant 6.9$ mg/24 h, an albumin excretion >6.9 mg/24 h carried a twofold increased risk, and >21 mg/24 h carried a 2.2-fold increased risk
Framingham Heart Study Offspring	Community residing adults without hypertension or diabetes *n*=1499	New-onset hypertension Increase in JNC-7 BP category	Risk of increased blood pressure was higher with increasing albumin/creatinine ratios using $\leqslant 1.7$ mg/g as the comparison group; for example, an albumin/creatinine ratio 1.7–3.8 mg/g was associated with a 90% increase in risk of developing hypertension
Framingham Heart Study Offspring	Community residing adults without hypertension or diabetes *n*=1568	Composite of CV death, MI, stroke, TIA, angina, CHF, or claudication	An albumin excretion $\geqslant 3.9$ mg/g in men and $\geqslant 7.5$ mg/g in women was associated with a threefold higher risk of incident CVD events
Nord-Trondelag Health Study	Community residing adults in Nord-Trondelag, Norway without baseline hypertension, diabetes, or CVD *n*=1989	Death	An albumin excretion $\geqslant 6.7$ mg/g was associated with a 2.3-fold increased risk of death

CHF=congestive heart failure; CHD=coronary heart disease; CV=cardiovascular; HOPE=Heart Outcomes Prevention Evaluation; LIFE=Losartan Intervention For Endpoint reduction in hypertension; MI=myocardial infarction; PREVEND=Prevention of Renal and Vascular ENd-stage Disease; TIA=transient ischemic attack.
[a]The PREVEND study did not normalize albumin excretions to creatinine.

Similar to cholesterol and blood pressure, there is a continuous relationship between the level of albumin excretion and the risk of cardiovascular events. The studies outlined in Table 2, especially the data from HOPE, LIFE, and Framingham, clearly suggest that only negligible amounts of albuminuria should be considered normal. Specifically, levels above approximately 2 mg/g of creatinine (or an estimated excretion rate of 2 mg/day) are significantly associated with cardiovascular death, myocardial infraction, stroke, and elevation in blood pressure.[57,58,63] The HOPE and LIFE results further suggest that this association applies to both diabetics and nondiabetics alike.[57,58]

Although no randomized trials have specifically addressed the question of whether a reduction in albuminuria would result in a concomitant reduction in renal and cardiovascular events, multiple observations suggest this may be true. Parving and colleagues showed that the degree of albuminuria reduction during the first year of therapy was the best predictor of slowing progression of renal disease in type I diabetics.[55,56] Among type II diabetics, the RENAAL investigators took advantage of a 6-month on-treatment re-evaluation of risk factors to determine if a decrease in albuminuria was associated with a favorable outcome.[68] After adjustment for multiple risk factors, a 30% or greater decrement in albumin excretion at 6 months was associated with a 35% reduction in the combined cardiovascular end point independent of the concomitant 6-month change in blood pressure, renal function, body size, or hemoglobin A1c.

In fact, among all risk-factor changes between baseline and 6 months, only persistent albuminuria was significantly predictive of cardiovascular events. Expressed as a continuous variable, every halving of albumin excretion was associated with an 18% lower risk of cardiovascular events. In a *post hoc* analysis of nondiabetics with kidney disease, the African American Study of Kidney Disease and Hypertension investigators examined whether 6-month on-treatment change in albuminuria predicted end-stage renal disease.[70] After adjustment for treatment arm and baseline albuminuria, a 20–50% reduction in albumin excretion at 6-months was associated with an approximate 50% lower risk of end-stage renal disease, and if albuminuria was lowered by more than half, the relative risk of end-stage renal disease was cut by almost 75%.

As with blood pressure, the available evidence argues that cardiovascular risk follows a continuous positive relationship with albumin excretion and that lowering albuminuria independently lowers the risk of renal and cardiovascular events.

WHAT IS NORMAL? A CENTRAL QUESTION WITH BROADER APPLICATION

The main thrust of this argument is that our current definitions of 'normal' for blood pressure and albuminuria are, in fact, abnormal, and that the terminology 'hypertension' and 'microalbuminuria' are misleading in suggesting dichotomy where associations are continuous. Observational data show that for both blood pressure and albuminuria, lower is clearly better in both high- and usual-risk individuals, whereas randomized trials illustrate benefit in treating high-risk individuals with 'normal' levels of blood pressure.

Because unguided pharmacotherapy is neither prudent nor feasible for clinicians and patients, and the risks of therapy must temper the absolute (rather than relative) benefits – which obviously differ by an individual's baseline risk of cardiovascular disease – the maintenance of guidelines employing categories of blood pressure and albuminuria is likely inevitable. Nevertheless, given that 'normal' is not normal, we urge that future randomized trials identify levels of blood pressure and albuminuria, below which further therapy is no longer beneficial.

In addition, we believe that our central question, 'what is normal', has broader applicability in clinical medicine, and should spark re-evaluation of 'normal' among a variety of parameters. For example, are risks associated with a fasting plasma glucose of 90 mg/dl the same as those associated with 125 mg/dl? Should the term 'impaired glucose tolerance' be re-evaluated? A body mass index of 24.9 imparts greater risk than a body mass index of 20 kg/m^2; should the arbitrary definition of 'normal' weight be changed? Many other examples probably exist. During the course of human history, our behavior and environment fell out of step from our genetic heritage, explaining the clinical benefits observed with closer proximity to paleo- rather than neo-normality.

REFERENCES

1. Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. A cooperative study. *JAMA* 1977; **237**: 255–261.
2. The 1980 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1980; **140**: 1280–1285.
3. The 1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1984; **144**: 1045–1057.
4. The 1988 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1988; **148**: 1023–1038.
5. The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). *Arch Intern Med* 1993; **153**: 154–183.
6. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1997; **157**: 2413–2446.
7. Chobanian AV, Bakris GL, Black HR *et al.* The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; **289**: 2560–2572.
8. Wang Y, Wang QJ. The prevalence of prehypertension and hypertension among US adults according to the new joint national committee guidelines: new challenges of the old problem. *Arch Intern Med* 2004; **164**: 2126–2134.
9. Viberti G, Pickup JC, Bilous RW *et al.* Correction of exercise-induced microalbuminuria in insulin-dependent diabetics after 3 weeks of subcutaneous insulin infusion. *Diabetes* 1981; **30**: 818–823.
10. Viberti GC, Hill RD, Jarrett RJ *et al.* Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. *Lancet* 1982; **1**: 1430–1432.
11. Svendsen PA, Oxenboll B, Christiansen JS. Microalbuminuria in diabetic patients – a longitudinal study. *Acta Endocrinol Suppl (Copenhagen)* 1981; **242**: 53–54.
12. Mathiesen ER, Ronn B, Jensen T *et al.* Relationship between blood pressure and urinary albumin excretion in development of microalbuminuria. *Diabetes* 1990; **39**: 245–249.
13. Morwood MJ, Brown P, Jatmiko *et al.* Further evidence for small-bodied hominins from the Late Pleistocene of Flores, Indonesia. *Nature* 2005; **437**: 1012–1017.
14. Oliver WJ, Cohen EL, Neel JV. Blood pressure, sodium intake, and sodium related hormones in the Yanomamo Indians, a 'no-salt' culture. *Circulation* 1975; **52**: 146–151.
15. Lowenstein FM. A study of blood pressure and body measurements in medical students in the Brazilian Amazon City Belem. *Cardiologia* 1961; **39**: 46–56.
16. Whyte HM, Yee IL. Serum cholesterol levels of Australians and natives of New Guinea from birth to adulthood. *Australas Ann Med* 1958; **7**: 336–339.
17. Whyte HM, Graham IA, De Wolfe MS. Body fat, blood pressure and serum cholesterol of Australian men. *Australas Ann Med* 1958; **7**: 328–335.
18. De Wolfe MS, Whyte HM. Serum cholesterol and lipoproteins in natives of New Guinea and Australians. *Australas Ann Med* 1958; **7**: 47–54.
19. Whyte HM. Body fat and blood pressure of natives in New Guinea: reflections on essential hypertension. *Australas Ann Med* 1958; **7**: 36–46.
20. Casley-Smith JR. Blood pressures in Australian aborigines. *Med J Aust* 1959; **46**: 627–633.
21. Maddocks I. Blood pressures in Melanesians. *Med J Aust* 1967; **1**: 1123–1126.
22. Fleming-Moran M, Santos RV, Coimbra Junior CE. Blood pressure levels of the Surui and Zoro Indians of the Brazilian Amazon: group- and sex-specific effects resulting from body composition, health status, and age. *Hum Biol* 1991; **63**: 835–861.
23. Ghesquiere JL, Karvonen MJ. Some anthropometric and functional dimensions of the pygmy (Kivu Twa). *Ann Hum Biol* 1981; **8**: 119–134.
24. Hollenberg NK, Martinez G, McCullough M *et al.* Aging, acculturation, salt intake, and hypertension in the Kuna of Panama. *Hypertension* 1997; **29**: 171–176.
25. Diamond JM. Human evolution. Diabetes running wild. *Nature* 1992; **357**: 362–363.
26. Sharma AM. The thrifty-genotype hypothesis and its implications for the study of complex genetic disorders in man. *J Mol Med* 1998; **76**: 568–571.
27. James G, Baker P. *Human Population Biology and Blood Pressure: Evolutional and Ecological Considerations and Interpretations of Population Studies*, 2nd edn. Raven Press: New York, 1995.
28. Page LB. Epidemiologic evidence on the etiology of human hypertension and its possible prevention. *Am Heart J* 1976; **91**: 527–534.

29. Hollenberg NK, Martinez G, McCullough M *et al.* Aging, acculturation, salt intake, and hypertension in the Kuna of Panama. *Hypertension* 1997; **29**: 171–176.
30. Executive Summary of The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; **285**: 2486–2497.
31. Grundy SM, Cleeman JI, Merz CN *et al.* Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Arterioscler Thromb Vasc Biol* 2004; **24**: e149–e161.
32. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003; **326**: 1423.
33. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360**: 7–22.
34. Cannon CP, Braunwald E, McCabe CH *et al.* Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; **350**: 1495–1504.
35. Rose G. Sick individuals and sick populations. *Int J Epidemiol* 2001; **30**: 427–432 (discussion 433–424).
36. MacMahon S, Neal B, Rodgers A. Hypertension – time to move on. *Lancet* 2005; **365**: 1108–1109.
37. Anderson TW. Re-examination of some of the Framingham blood-pressure data. *Lancet* 1978; **2**: 1139–1141.
38. Stewart IM. Relation of reduction in pressure to first myocardial infarction in patients receiving treatment for severe hypertension. *Lancet* 1979; **1**: 861–865.
39. Untreated mild hypertension. A Report by the Management Committee of the Australian Therapeutic Trial in Mild Hypertension. *Lancet* 1982; **1**: 185–191.
40. Cooper SP, Hardy RJ, Labarthe DR *et al.* The relation between degree of blood pressure reduction and mortality among hypertensives in the Hypertension Detection and Follow-Up Program. *Am J Epidemiol* 1988; **127**: 387–403.
41. Jafar TH, Stark PC, Schmid CH *et al.* Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. *Ann Intern Med* 2003; **139**: 244–252.
42. Berl T, Hunsicker LG, Lewis JB *et al.* Impact of achieved blood pressure on cardiovascular outcomes in the irbesartan diabetic nephropathy trial. *J Am Soc Nephrol* 2005; **16**: 2170–2179.
43. Kannel WB, Wilson PW, Nam BH *et al.* A likely explanation for the J-curve of blood pressure cardiovascular risk. *Am J Cardiol* 2004; **94**: 380–384.
44. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991; **265**: 3255–3264.
45. Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. *Kidney Int* 2002; **61**: 1086–1097.
46. Nissen SE, Tuzcu EM, Libby P *et al.* Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA* 2004; **292**: 2217–2225.
47. Lewington S, Clarke R, Qizilbash N *et al.* Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360**: 1903–1913.
48. MacMahon S, Peto R, Cutler J *et al.* Blood pressure, stroke, and coronary heart disease. Part 1. Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990; **335**: 765–774.
49. Yusuf S, Sleight P, Pogue J *et al.* Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000; **342**: 145–153.
50. Mehler PS, Coll JR, Estacio R *et al.* Intensive blood pressure control reduces the risk of cardiovascular events in patients with peripheral arterial disease and type 2 diabetes. *Circulation* 2003; **107**: 753–756.
51. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003; **362**: 782–788.
52. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. *Lancet* 2001; **358**: 1033–1041.
53. Svensson P, de Faire U, Sleight P *et al.* Comparative effects of ramipril on ambulatory and office blood pressures: a HOPE substudy. *Hypertension* 2001; **38**: E28–E32.
54. Wright Jr JT, Bakris G, Greene T *et al.* Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA* 2002; **288**: 2421–2431.
55. Ruggenenti P, Perna A, Loriga G *et al.* Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet* 2005; **365**: 939–946.
56. Sarnak MJ, Greene T, Wang X *et al.* The effect of a lower target blood pressure on the progression of kidney disease: long-term follow-up of the modification of diet in renal disease study. *Ann Intern Med* 2005; **142**: 342–351.
57. Gerstein HC, Mann JF, Yi Q *et al.* Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 2001; **286**: 421–426.
58. Wachtell K, Ibsen H, Olsen MH *et al.* Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: the LIFE study. *Ann Intern Med* 2003; **139**: 901–906.
59. Hillege HL, Fidler V, Diercks GF *et al.* Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 2002; **106**: 1777–1782.
60. Kistorp C, Raymond I, Pedersen F *et al.* N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. *JAMA* 2005; **293**: 1609–1616.
61. Klausen K, Borch-Johnsen K, Feldt-Rasmussen B *et al.* Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes. *Circulation* 2004; **110**: 32–35.
62. Klausen KP, Scharling H, Jensen G, Jensen JS. New definition of microalbuminuria in hypertensive subjects: association with incident coronary heart disease and death. *Hypertension* 2005; **46**: 1–5.
63. Wang TJ, Evans JC, Meigs JB *et al.* Low-grade albuminuria and the risks of hypertension and blood pressure progression. *Circulation* 2005; **111**: 1370–1376.
64. Arnlov J, Evans JC, Meigs JB *et al.* Low-grade albuminuria and incidence of cardiovascular disease events in nonhypertensive and nondiabetic individuals: the Framingham Heart Study. *Circulation* 2005; **112**: 969–975.
65. Romundstad S, Holmen J, Kvenild K *et al.* Microalbuminuria and all-cause mortality in 2089 apparently healthy individuals: a 4.4-year follow-up study. The Nord-Trondelag Health Study (HUNT), Norway. *Am J Kidney Dis* 2003; **42**: 466–473.
66. Rossing P, Hommel E, Smidt UM, Parving HH. Reduction in albuminuria predicts diminished progression in diabetic nephropathy. *Kidney Int Suppl* 1994; **45**: S145–S149.
67. Rossing P, Hommel E, Smidt UM, Parving HH. Reduction in albuminuria predicts a beneficial effect on diminishing the progression of human diabetic nephropathy during antihypertensive treatment. *Diabetologia* 1994; **37**: 511–516.
68. de Zeeuw D, Remuzzi G, Parving HH *et al.* Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. *Circulation* 2004; **110**: 921–927.
69. Ibsen H, Olsen MH, Wachtell K *et al.* Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients: losartan intervention for endpoint reduction in hypertension study. *Hypertension* 2005; **45**: 198–202.
70. Lea J, Greene T, Hebert L *et al.* The relationship between magnitude of proteinuria reduction and risk of end-stage renal disease: results of the African American study of kidney disease and hypertension. *Arch Intern Med* 2005; **165**: 947–953.